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Review Article

MANAGEMENT OF DEEP VENOUS THROMBOSIS

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Abstract:

Introduction: Acute unilateral leg swelling and/or pain is one of the most common complaints to be encountered in an emergency department (ED). The prompt responses is devoted to adequately Diagnose or eliminate the critical causes. Deep vein thrombosis has a high incidence as of 1 per 1000 person-year. When it comes to an emergency department, it has been estimated that about 10-25 percent of suspected cases would turn out to have a DVT. The concern of the presence of IC-DVT has emerged from the risk of thrombus propagation. Hence, development of A proximal DVT. This in turn, as stated earlier, has a higher risk of complication with pulmonary embolism or post-thrombotic syndrome.

Aim of work: In this review, we will discuss the recent available evidence regarding the management of DVT.

Methodology: We performed a systematic search for the management of deep venous thrombosis. The PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>) were the main search engine that has been used. We also included in our search the recent advancement and guidelines regarding the management of deep venous thrombosis.

Conclusions: Unilateral leg pain and/or swelling is a common ED complaint. The diagnosis of isolated calf vein DVT is particularly challenging when the Standard diagnostic modality, a whole-leg ultrasound WLUS, is not readily available. Treatment is controversial, universal versus selective anticoagulation. The risks of proximal progression and life-threatening embolization should be considered along the benign nature of a distal clot. An individual patient risk factors for both clot propagation and the complications of therapy should also be considered.

Key words: Deep venous thrombosis, emergency, management, screening and prevention.

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INTRODUCTION:

Acute unilateral leg swelling and/or pain is one of the most common complaints to be encountered in an emergency department (ED). The prompt responses are devoted to adequately Diagnose or eliminate the critical causes. Deep vein thrombosis (DVT) is usually one of the first causes that should be investigated. This is especially important with the proximal type of DVT, which carries a high risk of pulmonary embolism and its complications. Despite the exclusion of proximal DVT usually takes a place early, the isolated calf Deep Vein Thrombosis (IC-DVT) often remains in the list of differential diagnosis. This is attributed to the lack of Whole-leg duplex ultrasonography (WLUS) in the majority of ED, The gold standard to yield the diagnosis. This paucity of WLUS leads to postponement of the diagnosis for several hours.

Deep vein thrombosis has a high incidence as of 1 per 1000 person-year. When it comes to an emergency department, it has been estimated that about 10-25 percent of suspected cases would turn out to have a DVT. The isolated calf DVT was found to be in 11 percent of 1495 individuals had been suspected to have it in a community-based study [1]. After performing a Whole-leg duplex ultrasonography (WLUS), this percent went as high as 50 percent [2]. The concern of the presence of IC-DVT has emerged from the risk of thrombus propagation. Hence, development of A proximal DVT. This in turn, as stated earlier, has a higher risk of complication with pulmonary embolism or post-thrombotic syndrome. Thus, although these types of DVT differ in the carried risk on a short-term basis, the long-term outcomes are similar between them.

We aim in this review to discuss the recent available evidence regarding the management of DVT. In addition, we propose an algorithm for the evaluation of a patient with suspected IC-DVT in the lack of a Whole-leg duplex ultrasonography, and the treatment controversy of this entity.

METHODOLOGY:

We performed a systematic search for the management of deep venous thrombosis. The PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>) were the main search engine that has been used. We also included in our search the recent advancement and guidelines regarding the management of deep venous thrombosis. All relevant studies were retrieved and discussed. We only have included the full articles available.

The key terms have been used in our search are Deep venous thrombosis, management, surgery, and emergency.

The Risk of propagation, pulmonary embolism and the mortality in the isolated calf DVT.

It has been assumed that the vast majority of DVT, including the proximal types, were started in the calf veins, i.e. more distal. Then, it propagates to more proximal veins such as popliteal or femoral veins for instance. This propagation from untreated, symptomatic calf thrombus is found to be happening in about 16% of the time [3,4]. Yet, the propagation has not been encountered after the period of two weeks [5]. The risk factor favors this extension varies. The positive D-dimer, the presence of malignancy or history of it, a previous thromboembolic event, the large size of the thrombus and its closeness to proximal veins in addition to prior trauma. In addition to lack of the reversible provoking factors, all of these are associated with higher incidence of propagation.

Although it is common, the mortality of IC-DVT is still rare and was accounted to be less than 1%. However, the association between the benign IC-DVT and more serious complications as pulmonary embolism is being investigated. It was found that when the search of DVT was begun after the diagnosis of PE had been made, about 10% of cases turned to have IC-DVT. 18 From the other hand, 13% of patient with IC-DVT would have asymptomatic PE if they tested.18 This relation is currently undergoing active discussion, and will not be addressed in this review [6,7].

How Should the Diagnosis of Suspected IC-DVT Be Approached?

The approach to suspected IC-DVT is best to be done by using the Whole-leg duplex ultrasonography (WLUS). When WLUS rules out the IC-DVT, The risk of subsequent composition of venous thromboembolism (VTE) complication is less than 1% [8]. When WLUS is not readily available, the alternative modalities to be used are the proximal compression ultrasonography –whether bedside or at radiology department, the clinical probability assessments, and the D-dimer status.

Combining the Clinical probability (Wells Score) and D-dimer test could be helpful. In low-risk patients (Wells score of 0 or less), the D-dimer test has a high negative predictive value that has been estimated to be as high as 99% or more [9]. This is true for DVT in general, as well as IC-DVT. The Clinical Practice Guidelines for Antithrombotic Therapy and

prevention of thrombosis published in 2012 by American College of Chest Physicians (ACCP) endorsed the combination of these two methods in ruling out DVT of the lower extremity. Hence, when the D-dimer is negative and the pretest probability (using Wells score) is low, there is no benefit from further testing. This is supported by Wells et al. 2003, 2006 and ACCP 2012 guideline. However, when the D-dimer is positive, the ACCP guideline recommends the using of proximal compression ultrasound.

In the absence of WLUS, and The presence of positive D-dimer or moderate to a high probability using the Wells score, prompt the use of compression Ultrasound (CUS) in the emergency department to rule out proximal DVT. A positive test by CUS would recognize the need for therapeutic anticoagulation. The significant increase in trained ED physicians to utilize the CUS made this modality more accessible in the bedside rather than the need for radiological studies. This is especially important after the end of ordinary working hours.

The sensitivity of bedside CUS has been assessed by multiple studies, it was estimated to be about 95 – 99 percent.¹⁰⁻¹¹ Nevertheless, The classical CUS remains an option in case it is available. When combining the negative D-dimer result with a bedside CUS, the modality is adequately effective in excluding the vast majority of clinically important DVT, with estimated NPV to be more than 99%. This alternative is particularly important in patients with moderate to high pretest probability.

IC-DVT in the Setting of Positive D-dimer and Negative CUS for Proximal DVT.

WLUS remains the definitive diagnostic test when the D-dimer resulted to be positive and CUS is negative. When WLUS is deficient and not readily available, the ACCP guideline recommends two alternative strategies (presented in the Figure). The first is a direct imaging of the calf veins using a short-term definitive whole-leg ultrasound. From the other hand, repeating the proximal CUS after one week to assess proximal progression could be an alternative.⁵ This repetition of CUS after a single week has been found to be equivalent to a single WLUS in excluding IC-DVT that carries the likelihood of progression. Furthermore, it is safe (0-1.8% VTE at 3-6 months) [12]. This would aid the ED patients whom the routine follow up as an outpatient is not reliable for any reason. Now, returning to ED to repeat bedside CUS would be an option.

After excluding proximal DVT in the ED and the possibility of IC-DVT is being investigated either by planned short-term deferred WLUS or repeated proximal CUS, the practice of providing a bridge of empiric anticoagulation between imaging studies is not supported [13,14].

Treatment of Confirmed IC-DVT - Selective Anticoagulation.

After presenting a suggested algorithm for the diagnosis of IC-DVT in lack of immediate WLUS. We will briefly review the controversy about IC-DVT treatment [15,16]. The previously mentioned ACCP guidelines, the current European guidelines, and the currently available evidence all of which have recommended treating IC-DVT with at least three months of anticoagulation [17,18]. The latest ACCP guidelines include a more selective approach. The controversy regarding the different approaches is best exemplified by a survey of faculty physicians in one of major U.S medical center. Half of the respondents chose the “routinely use anticoagulation to treat venous thrombosis below the knee” and half did not [19]. This controversy over treatment approaches is largely derived from the increased frequency of diagnosed IC-DVT, coupled with the belief that the distal DVT is less concerning than proximal. In addition, the risk factors associated with it are more likely to be transient and reversible. Nevertheless, the mortality and recurrence rates are scanty.²⁰ Physicians who prefer the observation strategy over the treatment approach argue to support their decision by the fact that the majority of patients with negative proximal DVT by CUS –even if they have missed IC-DVT- would have an acceptable outcome without treatment. These accepted outcomes outweigh the possible complication by treatment approach as a bleeding for an example. As the case of our patient.

There is a universal demand for a large randomized trial to address this question. In response to this critical question, a promising trial is currently ongoing (www.ClinicalTrials.gov) [21]. Until now, in the absence of a definitive answer, recommendation, as suggested by the ACCP, to base the treatment decision on risks/benefits analysis and shared decision-making is widely used.

Treatment of Confirmed IC-DVT - Shared Decision-Making.

The ACCP Current guideline based on the best available evidence (currently in their 10th edition, spanning 30 years) has suggested a solid point for the clinical decision-making process [22] the latest edition has proposed two options to deal with

confirmed IC-DVT: The first of which is the use of therapeutic anticoagulation; the second is a weekly-based follow-up with compression ultrasonography (CUS) for two weeks to monitor proximal thrombus propagation. The use of anticoagulation is reserved for severely symptomatic patients and/or those with higher risk factors for proximal extension should. Patients who are carrying a high risk of anticoagulation-associated major bleeding may be managed by follow up. In Contrast, patients with a lower risk of both propagation and hemorrhage may greatly benefit a more selective approach using shared decision-making [23]. The discussion should be well documented and focuses on the patient's judgment and readiness to comply with serial surveillance for clot propagation versus their tolerance for the risks of bleeding associated with the medication. Given the controversy over IC-DVT management, a primary provider and/or a consultant should be involved in the decision-making whenever it is possible. In addition to their effort to assure a close follow up. There is a lack of data regarding either strategy for IC-DVT in patients with a variable level of risks.

Additional therapeutic modality.

There is no evidence regarding the use of gradual compression stocking neither for symptomatic relief nor for its role in preventing post-thrombotic syndrome (PTS) in the cases of IC-DVT. However, regarding the proximal DVT, the reported adverse events from using these stockings are rare, and their value for PTS preventions is uncertain [24,25]. No recommendations could be found for the role of aspirin in the management of IC-DVT.

Surgical interventions: Pulmonary embolectomy and IVC filters.

Pulmonary embolectomy.

The ACCP guideline suggests an initial management of PE by surgical pulmonary embolectomy only in massive cases, which should be documented by angiography whenever it is possible. This massive PE includes the failure of heparin and resuscitation efforts, thrombolytic therapy or a contraindication to its use. To date, no randomized trials evaluating this have been found. Stein et al. Pooled data has shown about 20% of mortality rate related to operation in patients undergoing pulmonary embolectomy between 1985 and 2005, compared with 32% before 1985.²⁹ A more recent retrospective study included a 214 patients undergoing surgical embolectomy for massive and submassive PE has found in-hospital mortality rate to be 11.7%. The highest death rate was (32.1%) in patients with preoperative cardiac arrest. Surgical embolectomy in patients with

intermediate to high-risk conditions (defined as elevated biomarkers and evidence of right heart strain on computed tomographic angiography or echocardiography) has also been reported [26].

IVC filters.

Current recommendation precludes the routine use of IVC filters for patients with DVT or PE who are suitable for management with anticoagulants. However, in the presence of contraindication to anticoagulant, complications of its usage, recurrent thromboembolism events despite adequate anticoagulant therapy, and the use of IVC become absolute indications. Nevertheless, the relative indications for IVC filters include massive PE; ilio caval DVT; free-floating proximal DVT; cardiac or pulmonary insufficiency; a high risk of complications from anticoagulation (frequent falls, ataxia); and poor compliance to the treatment.

When the anticoagulant is temporary contraindicated or in case of a short duration of PE risk, the retrievable IVC filter is an adequate consideration.²⁷ The consensus guidelines advise the same indications for placing a retrievable IVC filter as well as a permanent device. The IVC filter by itself is not an effective therapy for VTE, and resumption of anticoagulation is recommended as soon as possible after its placement.

SCREENING AND PREVENTION

More than half of all VTE events occur in hospitals and nursing homes [28]. Yet, the use of anticoagulant prophylaxis greatly differed among hospitalized patients for medical conditions versus a hospitalized patients for surgical one. The estimated percent of at-risk patients who have been managed by anticoagulant was 16 to 33 among the medical hospitalized versus a 90% of surgical [29] a meta-analysis involving 19,958 patients has showed that Adequate prophylaxis can reduce the incidence of VTE., with a Relative Risk reduction of 64% of fatal PE, 58% for symptomatic PE, and a 53% reduction for a symptomatic DVT

The consequences of VTE include symptomatic DVT and PE whether fatal or symptomatic, the cost of investigating symptomatic patients, the risk and cost of treatment (e.g. bleeding), PTS, and chronic thromboembolic pulmonary hypertension.

Heparin, enoxaparin, and fondaparinux are approved drugs for prophylaxis use. However, the indication of these drugs varies. For example, factor Xa inhibitors, rivaroxaban, and apixaban were approved for prophylaxis in patients undergoing total knee or hip

replacement.

Recently, the factor Xa inhibitor, betrixaban, has been approved for VTE prophylaxis up to 42 days in a hospitalized adult suffering an acute medical illness.⁴⁴ Patients with a high risk of bleeding who are unable to receive pharmacologic prophylaxis, intermittent pneumatic compression devices or graduated compression stockings should be used as an alternative.

Compression stockings

In patients with DVT, ACCP guideline advises against the routine use of compression stockings as preventive measure. While the current evidence suggests that compression stockings is not effective measure for PTS prevention, they may reduce the symptoms of acute or chronic DVT in some patients.

LIMITATIONS

The significant variation in overall and subset types of DVT is a major drawback. Despite the large number of available reports, many of them are derived from small underpowered observational cohort studies. A Subsequent meta-analysis has tried to combine the data of these studies. The plausible explanations of this observed variability include the size and heterogeneity of the patient sample. Whether they were inpatient, outpatient, community-based sample, post-surgical, traumatic, presence or absence of symptoms, the reason for testing (suspected or confirmed PE, versus DVT), and the diagnostic imaging modality had been used. Most series did not image the entire leg.

Another limitation is the fact that the suggested algorithm was based on the latest evidence and practice guidelines. When the literature is rich in papers discussing this topic, the lack of prospective controlled evaluation makes the current evidence of low quality. A prospective controlled trial would be essential.

The loss of follow up in almost all the strategies concerned about surveillance approaches is an important factor to be considered. During the period covered by this discussion, D-dimer assays evolved and the Wells clinical prediction rules were modified. The current recommendations are based on the use of highly sensitive D-dimer assay. there is a variable types of assays in the practical situation.⁵⁸ Both the Wells criteria and D-dimer assays have greater sensitivity for proximal than isolated distal DVT [30].

Leg pain and swelling are among the common ED complaints that trigger a search for serious conditions

requiring urgent intervention. Yet, less than 25% of these patients would have DVT. Even after applying the clinical decision rules and performing the diagnostic tests with a high sensitivity as well as 99 percent, the physicians would encounter a false negative with serious consequences. The literature is rich in many cases as an example of this [31].

CONCLUSION:

Unilateral leg pain and/or swelling is a common ED complaint. The diagnosis of isolated calf vein DVT is particularly challenging when the Standard diagnostic modality, a whole-leg ultrasound WLUS, is not readily available. A proposed diagnostic algorithm to be used in the ED is presented. The algorithm has been based on the most recent recommendations of the American College of Chest Physicians (ACCP). It is important to carry in mind that this algorithm is based on a critical appraisal of the current evidence in the literature. The current evidence lacks the adequate strength, and prospective controlled studies still required before it can be recommended for a widespread implementation. Treatment is controversial, universal versus selective anticoagulation. The risks of proximal progression and life-threatening embolization should be considered along the benign nature of a distal clots. Individual patient risk factors for both clot propagation and the complications of therapy should also be considered.

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